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CADTH Reimbursement Recommendation

Daunorubicin and Cytarabine (Vyxeos)

Indication: Treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)

Sponsor: Jazz Pharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Vyxeos?

CADTH recommends that Vyxeos should be reimbursed by public drug plans for the treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) if certain conditions are met.

What Are the Conditions for Reimbursement?

Vyxeos should only be reimbursed if the induction cycles are administered in an inpatient setting and supervised by a hematologist with expertise in managing patients with acute leukemia and if the cost of Vyxeos is reduced.

Which Patients Are Eligible for Coverage?

Vyxeos should only be covered to treat adult patients with newly diagnosed t-AML or AML-MRC who were deemed fit for intensive chemotherapy by the treating physician.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical study showed that Vyxeos prolonged life — one of the needs important to patients — and improved remission rates in patients with newly diagnosed t-AML or AML-MRC compared to conventional cytarabine and daunorubicin (7 + 3).
- Based on public list prices, Vyxeos is not considered cost-effective compared to 7 + 3 at a willingness-to-pay (WTP) threshold of $50,000 per QALY. Economic evidence suggests that a 68% price reduction or greater is needed to ensure Vyxeos is cost-effective at that WTP threshold.
- Based on public list prices, the estimated 3-year budget impact is $34,304,171 if the cost of Vyxeos is covered by participating drug plans for inpatients.
- Cost-effectiveness and price reduction estimates are likely biased in favour of Vyxeos due to structural limitations in the pharmacoeconomic model. The cost-effectiveness of Vyxeos is unknown compared with FLAG-IDA and 7 + 3 with midostaurin, and in patients younger than 60 years or older than 75 years.

Additional Information

What Is t-AML and AML-MRC?

AML is a cancer of the blood and bone marrow that leads to fewer mature blood cells. Patients with t-AML or AML-MRC have a worse prognosis compared with patients with other subtypes of AML. AML is rare; it represents approximately 1% of all cancer diagnoses.

Unmet Needs in t-AML and AML-MRC

Current treatments are associated with several side effects and are of limited effectiveness. Treatments are needed that prolong survival, maintain remission, and have an acceptable side-effect profile and a favourable impact on quality of life.

How Much Does Vyxeos Cost?

Treatment with Vyxeos is expected to cost approximately $46,642 for a first induction cycle, $31,094 for a second induction cycle, and $31,094 for each consolidation cycle (cycle length is 28 days).

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that liposomal daunorubicin and cytarabine should be reimbursed for the treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 open-label, phase III, randomized controlled trial (Study 301, N = 309) in adult patients (60 years to 75 years of age) with newly diagnosed t-AML or AML-MRC demonstrated that liposomal daunorubicin and cytarabine was associated with a statistically significant and clinically meaningful greater overall survival (OS) rate (median = 9.56 months; 95% confidence interval [CI], 6.60 to 11.86) compared with the control group, which consisted of conventional cytarabine and daunorubicin (7 + 3) (median = 5.95 months; 95% CI, 4.99 to 7.75). Treatment with liposomal daunorubicin and cytarabine also lowered the risk of death by 31% compared with the control group (hazard ratio [HR] = 0.69; 95% CI, 0.52 to 0.90; 1-sided P = 0.003). At a 5-year follow-up, 18% of patients who received liposomal daunorubicin and cytarabine were alive compared with 8% of those who received 7 + 3, with a median OS in the liposomal daunorubicin and cytarabine treatment group of 9.33 months and 5.95 months in the 7 + 3 treatment group. Liposomal daunorubicin and cytarabine was also associated with a statistically significant higher remission rate (complete remission [CR] or CR with incomplete neutrophil or platelet recovery [CRi]) compared with the 7 + 3 treatment group: 74 patients (47.7%) in the liposomal daunorubicin and cytarabine treatment group and 52 patients (33.3%) in the 7 + 3 treatment group achieved a CR or CRi (OR = 1.77; 95% CI, 1.11 to 2.81; 1-sided P = 0.008). A need identified by patients as important was prolonging life; pERC concluded that this need was met with liposomal daunorubicin and cytarabine treatment. Patients also valued an outpatient treatment option that is accessible and closer to their home; however, the induction cycles of liposomal daunorubicin and cytarabine are administered in an inpatient setting. Other needs identified by patients, including maintaining health-related quality of life (HRQoL), were either unmet by liposomal daunorubicin and cytarabine or the evidence was not available.

Liposomal daunorubicin and cytarabine costs $7,774 per vial, and each vial contains 44 mg of daunorubicin and 100 mg of cytarabine. The recommended dose of liposomal daunorubicin and cytarabine is 100 units/m^2 (equivalent to 44 mg/m^2 of daunorubicin and 100 mg/m^2 of cytarabine) of body surface area resulting in a 28-day cycle cost of $46,642 for first induction and $31,094 for a second induction. The recommended dosage for consolidation therapy is 29 mg/m^2 of daunorubicin and 65 mg/m^2 of cytarabine, for a cost of $31,094 per consolidation cycle. Using the sponsor-submitted price for liposomal daunorubicin and cytarabine and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for liposomal daunorubicin and cytarabine was $110,283 per quality-adjusted life-year (QALY) compared with 7 + 3. At this ICER, liposomal daunorubicin and cytarabine is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for adults with newly diagnosed t-AML or AML-MRC. A reduction in price of at least 68% is required for liposomal daunorubicin and cytarabine to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Adults with newly diagnosed t-AML or AML-MRC.	Patients enrolled in Study 301 were adults with newly diagnosed t-AML or AML-MRC
2. Patients must be deemed fit for intensive chemotherapy by the treating physician.	The clinical experts noted that patients who are considered fit enough for induction with existing chemotherapy regimens (e.g., 7 + 3 or FLAG-IDA) would likely be considered adequately fit for liposomal daunorubicin and cytarabine.
Renewal	
3. Initial reimbursement of liposomal daunorubicin and cytarabine should be limited to 2 cycles of induction therapy.	Patients enrolled in Study 301 were eligible to receive up to 2 cycles of inductions and up to 2 cycles of consolidations of liposomal daunorubicin and cytarabine. The product monograph notes that treatment with liposomal daunorubicin and cytarabine should be continued as long as the patient continues to benefit or until disease progression up to a maximum of 2 induction courses and up to a maximum of 2 consolidation courses.
4. Patients who achieve CR or CRi during induction cycles are eligible for reimbursement of up to an additional 2 cycles of consolidation therapy with liposomal daunorubicin and cytarabine.	In Study 301, patients who achieved CR or CRi after 1 or 2 induction cycles were eligible to receive up to 2 cycles of consolidation therapy. The clinical experts noted that a CR or CRi is the prerequisite to move forward with further cycles of consolidation chemotherapy.
Prescribing	
5. The induction cycles of liposomal daunorubicin and cytarabine should be administered in an inpatient setting and supervised by a hematologist with expertise in managing patients with acute leukemia.	The clinical experts noted that administration of induction therapies, including liposomal daunorubicin and cytarabine, is conducted in inpatient settings with close monitoring by specialists during and after infusion. Support from transfusion specialists may be required, depending on patient status post-induction. In Study 301, patients were admitted to hospital during induction, and liposomal daunorubicin and cytarabine was administered to them as inpatients.
6. The consolidation cycles of liposomal daunorubicin and cytarabine can be administered in an outpatient setting.	The clinical experts noted that consolidation therapy may be administered in outpatient settings. However, this varied between practices across Canada, depending on local capacity. In Study 301, during consolidation, approximately half the patients in the liposomal daunorubicin and cytarabine treatment group were discharged and received their consolidation treatment in an outpatient infusion clinic.
7. Liposomal daunorubicin and cytarabine should not be used in combination with other anti-cancer therapy.	There is no evidence to demonstrate a benefit of liposomal daunorubicin and cytarabine in combination with other anti-cancer therapy for the treatment of adults with newly diagnosed t-AML or AML-MRC

Reimbursement condition	Reason
Pricing	
8. Reduction in price	The ICER for liposomal daunorubicin and cytarabine is $110,283 per QALY compared with 7 + 3. A price reduction of at least 68% would be required for liposomal daunorubicin and cytarabine to achieve an ICER of $50,000 per QALY compared with 7 + 3, although this is likely underestimated.

AML-MRC = acute myeloid leukemia with myelodysplasia-related changes; CR = complete remission; CRi = complete remission with incomplete neutrophil or platelet recovery; FLAG-IDA = fludarabine, high-dose cytarabine, granulocyte-colony stimulating factor, and idarubicin; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; t-AML = therapy-related acute myeloid leukemia.

Implementation Guidance

1. The cost-effectiveness of liposomal daunorubicin and cytarabine is unknown in patients younger than 60 years of age and in patients older than 75 years of age. A further price reduction may be warranted given the uncertainty of effectiveness in these age groups.
2. The clinical experts noted to pERC that the criteria used to identify patients with t-AML or AML-MRC in Study 301 represent what is currently used in clinical practice.
3. The product monograph for liposomal daunorubicin and cytarabine provides stability information under refrigeration scenario only and not at room temperature. pERC noted that the short stability duration could affect the potential sites for outpatient administration during consolidation cycles and would also necessitate access to onsite pharmacy services for induction and consolidation therapy.

Discussion Points

- pERC discussed that a proportion of adult patients with t-AML or AML-MRC in Canada may be treated with a fludarabine, high-dose cytarabine, granulocyte-colony stimulating factor, and idarubicin combination regimen (FLAG-IDA) as an induction option, and that patients with *FLT3* mutations may be treated with 7 + 3 plus midostaurin. However, there is no direct or indirect evidence comparing liposomal daunorubicin and cytarabine with FLAG-IDA or 7 + 3 in combination with midostaurin.
- Study 301 enrolled only patients who were 60 years to 75 years of age; therefore, the Committee discussed whether the results are generalizable to younger or older patients who may otherwise be eligible for treatment with liposomal daunorubicin and cytarabine. However, the clinical experts noted that age alone is not an appropriate criterion to determine which patients would be eligible for induction therapy with liposomal daunorubicin and cytarabine, and that a patient's fitness would be a more appropriate indicator.
- pERC discussed that patients must be deemed fit for intensive chemotherapy by the treating physician to be eligible to receive induction therapy with liposomal daunorubicin and cytarabine. The clinical experts noted that patients considered fit enough for induction with existing chemotherapy regimens (e.g., 7 + 3 or FLAG-IDA) would likely be adequately

fit for liposomal daunorubicin and cytarabine. The clinical experts indicated that there is no universal definition of fitness; however, age, comorbidities, performance status, and organ dysfunction are associated with AML treatment determination.

- pERC discussed the number of induction and consolidation cycles that should be eligible for reimbursement. The clinical experts noted that, in clinical practice, patients receive up to 2 cycles of induction and up to 2 cycles of consolidation chemotherapy, and that it is rare that patients would receive more than 2 cycles of consolidation.
- In Study 301, the number of induction and consolidation cycles that patients received depended on response (CR or CRi), which was confirmed by a bone marrow assessment done on day 14 after each induction cycle. pERC discussed that bone marrow assessments vary across Canada and that many centres do not routinely do a day 14 bone marrow aspirate. The clinical experts' input to pERC was that, in clinical practice, assessment of CR occurs between 28 days and 35 days post-induction and includes the assessment of bone marrow, extramedullary disease, and complete blood count.
- The patient groups' input to CADTH highlighted that patients need a treatment that maintains their HRQoL. HRQoL was not measured in Study 301; therefore, pERC was unable to draw any conclusions pertaining to the potential benefit of liposomal daunorubicin and cytarabine on HRQoL.
- The Committee noted that a majority of the predicted incremental clinical benefit (QALYs) were predicted to occur after patients had experienced relapse. Although CADTH noted that this apparent bias is often seen in models of this type, pERC noted that the size of the implied benefit was larger than normal, and larger than the evidence supported by Study 301. Neither pERC nor CADTH could estimate the extent to which this was due to model structure, increased survival for patients receiving transplant, or some other factor. Consequently, the ICER and required price reduction are likely underestimated.
- The Committee discussed the substantial difference in budget impact when including the cost of liposomal daunorubicin and cytarabine when administered in the inpatient setting. The CADTH base case estimate for the budget impact assessment excluded costs of liposomal daunorubicin and cytarabine when administered on an inpatient basis; however, input from the Provincial Advisory Group (PAG) indicated that if liposomal daunorubicin and cytarabine is listed, most jurisdictions are likely to cover the costs of these drugs through their current cancer funding programs. A scenario analysis that is inclusive of inpatient costs estimates a 3-year budget impact of $34,304,171.
- The sponsor's pharmacoeconomic model did not include FLAG-IDA as a comparator. Consequently, the cost-effectiveness of liposomal daunorubicin and cytarabine compared with FLAG-IDA is unknown.

Background

Liposomal daunorubicin and cytarabine has a Health Canada indication for the treatment of adults with newly diagnosed t-AML or AML-MRC. Liposomal daunorubicin and cytarabine is a combination of daunorubicin and cytarabine, in a 1:5 molar ratio, encapsulated in liposomes for IV administration. Cytarabine is a cytidine analogue that interferes with DNA synthesis, and daunorubicin is anthracycline antibiotic that intercalates between DNA base pairs and interferes with DNA repair. Liposomal daunorubicin and cytarabine is available as an IV infusion; each vial contains 44 mg of daunorubicin and 100 mg of cytarabine. The

Health Canada–approved dose for induction is daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 administered intravenously over 90 minutes on days 1, 3, and 5 as the first course of induction therapy, and on days 1 and 3 as a subsequent course of induction therapy, if needed. For consolidation, the recommended dosing schedule of liposomal daunorubicin and cytarabine is daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 administered intravenously over 90 minutes on days 1 and 3 as subsequent courses of consolidation therapy, if needed.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a review of 1 phase III randomized controlled trial that included patients aged 60 years to 75 years with newly diagnosed t-AML or AML-MRC
- patients' perspectives gathered by 1 patient group: the Leukemia and Lymphoma Society of Canada (LLSC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 3 clinical specialists with expertise diagnosing and treating patients with t-AML or AML-MRC
- input from 2 clinician groups, including the Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO's DAC) and the Canadian Leukemia Study Group (CLSG)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Patient input was provided by LLSC through an English- and French-language online survey from December 7, 2020, through January 24, 2021. Patients were asked to describe their experiences with treatment for AML. In total, 29 individuals responded; all respondents identified as patients and all lived in Canada. No breakdown was provided on the proportions of patients with AML-MRC or t-AML.

Patients reported how AML symptoms affected their daily lives, including losing the ability to work, impacting social lives and relationships, and numerous detrimental effects on their health. Patients reported being easily fatigued, losing vision in one eye, nausea, bruising, numbness or body aches, and being immunocompromised. Many respondents indicated that they felt physically and socially isolated, and those who had completed therapy identified a concern about relapse.

Patients listed physician recommendation as the most important factor when deciding on new treatments, which was followed by possible impact on disease, quality of life, closeness to home, and outpatient treatment.

In general, respondents would like new therapies with fewer side effects, which are more holistic, would help maintain their remission, were covered through drug plans, and were accessible closer to their home. Patients were also interested in having more information on emerging therapies and being able to access all possible treatments in the future.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH for this review described how patients in this population are high-risk individuals with high unmet needs. Existing induction and consolidation therapies were described by the experts as not meeting the needs of all patients, resulting in many individuals not achieving remission and thus being ineligible for hematopoietic stem cell transplantation (HSCT). The drug under review is intended to act at the same step of the clinical pathway in patients with AML-MRC or t-AML who are fit enough for induction therapy. Survival, as well as response to induction therapy, was highlighted as a key outcome of interest. CR or CRi are influential on decisions for a subsequent HSCT, which was reported by the experts to confer a survival benefit.

Clinician Group Input

Two clinician groups provided input to this review: OH-CCO's DAC and the CLSG. Broadly, there was good concordance in the input between the clinical experts consulted by CADTH for this review and the clinician group regarding patient populations of interest, their unmet needs, and the outcomes of importance in this population. The clinician groups identified that the proposed product would act in a similar role as and replace existing 7 + 3 therapy.

Drug Program Input

The drug program had questions surrounding alternative therapies because only evidence of liposomal daunorubicin and cytarabine relative to 7 + 3 was identified, although FLAG-IDA is also used in practice in Canada. No data were identified for FLAG-IDA, and the clinical experts were uncertain about the relative effects of liposomal daunorubicin and cytarabine versus FLAG-IDA. PAG inquired about the efficacy of azacitidine ± venetoclax compared with liposomal daunorubicin and cytarabine. The clinical experts indicated that azacitidine ± venetoclax is reserved for patients who are not candidates for induction therapy, and patients who are treated with azacitidine ± venetoclax are different patient populations than those who are treated with 7 + 3, FLAG-IDA, or liposomal daunorubicin and cytarabine. PAG also inquired about eligible populations. The clinical experts indicated that the criteria used to enrol patients in Study 301 were representative of patients identified in practice. The clinical experts also noted that for patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of greater than 2, if the ECOG status was assessed to be related to AML status, patients would be considered for treatment in this context with an available induction regimen. It was also noted that patients younger than 60 years would be considered for treatment with liposomal daunorubicin and cytarabine, while patients older than 75 years would be considered if they were appropriately fit, although it was highlighted that this may not be common in practice. It was noted that patients with myeloproliferative neoplasm or combined myelodysplastic syndrome/myeloproliferative neoplasm, with the exception of a small proportion of patients with chronic myelomonocytic leukemia, were not included in Study 301; therefore, it is uncertain how these patients would respond to liposomal daunorubicin and cytarabine. It was also noted that patients with active central nervous system leukemia would likely be considered for treatment

with liposomal daunorubicin and cytarabine. Patients with favourable cytogenetics would still be treated with 7 + 3 if they were candidates for induction therapy and would also be considered for treatment with liposomal daunorubicin and cytarabine. Some patients with favourable cytogenetics are treated with 7 + 3 for induction followed by high-dose cytarabine with or without gemtuzumab. For patients treated in combination with other therapies (e.g., midostaurin), it was highlighted that this could occur off-label. Gemtuzumab was not considered a likely candidate for combination therapy. PAG also inquired whether liposomal daunorubicin and cytarabine could be used off-label, for example, in patients with other AML subtypes and other lines of therapy. The clinical experts noted it was unlikely that liposomal daunorubicin and cytarabine would be used in other AML subtypes. Receiving liposomal daunorubicin and cytarabine in another line of therapy was considered to be very unlikely. PAG inquired whether patients who are currently on 7 + 3 or FLAG-IDA would be switched to liposomal daunorubicin and cytarabine; the clinical experts noted that this switch is unlikely in the majority of cases. This may be relevant for a small number of patients during the window when compassionate use ends, and approval (if provided) is given. No specific cut-off point was identified.

Clinical Evidence

Clinical Trials

Description of Studies

One study, Study 301, was identified and included in the review. Study 301 was a phase III, randomized, controlled, multi-centre, open-label, therapy-controlled clinical trial that recruited 309 patients across 39 centres, 4 of which were based in Canada. Study 301 enrolled patients who were 60 years to 75 years of age and had a pathological diagnosis of AML according to WHO criteria (with at least 20% blasts in the peripheral blood or bone marrow) and had either newly diagnosed t-AML, AML with antecedent MDS, AML with antecedent chronic myelomonocytic leukemia, or de novo AML with MDS-related cytogenetic abnormalities defined per 2008 WHO criteria. Patients were randomly assigned to either liposomal daunorubicin and cytarabine (n = 153) or 7 + 3 (n = 156).

The primary outcome was OS; secondary end points included response, event-free survival (EFS), remission duration, and proportion of patients who received an HSCT. Response was defined as achieving CR or CRi during the treatment phase. CR was defined as bone marrow blasts less than 5%, absence of blasts with Auer rods, absence of extramedullary disease, absolute neutrophil count greater than 1.0×10^9/L (1,000/μL), platelet count greater than 100×10^9/L (100,000/μL), and independence from red cell transfusions; CRi was defined as all CR criteria except for residual neutropenia (< 1.0×10^9/L [1,000/μL]) or thrombocytopenia (< 100×10^9/L [100,000/μL]). EFS was defined as the time from study randomization to the date of induction treatment failure (persistent disease), relapse from CR or CRi, or death from any cause, whichever occurred first. Remission duration was measured from the date of achievement of remission (CR or CRi) until the date of relapse or death from any cause. All outcomes which had formal statistical assessments were conducted using a hypothesis-testing cut-off alpha value of 0.025 (1-sided).

Patients within this study had a mean age of 67.7 years (SD = 4.14), were predominantly male (190 of 309 patients, 61%), and the most common AML subtype included was AML-MRC

with prior hypomethylating agent exposure (105 of 309 patients, 34%). Seventy-two patients (50.3%) in the liposomal daunorubicin and cytarabine treatment group and 83 patients (56.8%) in the 7 + 3 treatment group had unfavourable cytogenetic risk, while 64 patients (44.8%) in the liposomal daunorubicin and cytarabine treatment group and 58 patients (39.7%) in the 7 + 3 treatment group had intermediate cytogenetic risk. The median duration of follow-up was similar between the treatment arms, with a median follow-up time of 20.5 months for patients treated with liposomal daunorubicin and cytarabine and 21.22 months for patients treated with 7 + 3.

Efficacy Results

The primary outcome, OS, was assessed in 153 patients who were randomized to the liposomal daunorubicin and cytarabine treatment group and 156 patients who were randomized to the 7 + 3 treatment group (intention-to-treat population). The median OS in the liposomal daunorubicin and cytarabine treatment group was 9.56 months (95% CI, 6.60 to 11.86) and 5.95 months (95% CI, 4.99 to 7.75) in the 7 + 3 treatment group. In the 153 patients assigned to the liposomal daunorubicin and cytarabine treatment group, there were 104 events; in the 156 patients assigned to the 7 + 3 treatment group, there were 132 events. There was a statistically significant improvement in OS in the liposomal daunorubicin and cytarabine treatment group compared with the 7 + 3 treatment group (HR = 0.69; 95% CI, 0.52 to 0.90; 1-sided log-rank test P = 0.003). At a 5-year follow-up, 18% of patients who received liposomal daunorubicin and cytarabine were alive versus 8% who received 7 + 3, with median OS of 9.33 months and 5.95 months in the liposomal daunorubicin and cytarabine treatment group and the 7 + 3 treatment group, respectively (HR = 0.70; 95% CI, 0.55 to 0.91). However, results from the 5-year follow-up are considered descriptive and should be interpreted with caution.

The median EFS was higher in the liposomal daunorubicin and cytarabine treatment group (median = 2.53 months; 95% CI, 2.07 to 4.99) than in the 7 + 3 treatment group (median = 1.31 months; 95% CI, 1.08 to 1.64), resulting in a statistically significant HR of 0.74 (95% CI, 0.58 to 0.96; 1-sided log-rank test P = 0.011).

For response rates, 73 patients (47.7%) in the liposomal daunorubicin and cytarabine treatment group achieved a CR or CRi versus 52 patients (33.3%) in the 7 + 3 treatment group. The liposomal daunorubicin and cytarabine treatment group was associated with a statistically significant higher response compared with the 7 + 3 treatment group (odds ratio [OR] = 1.77; 95% CI, 1.11 to 2.81; 1-sided P = 0.008).

There was no statistically significant difference observed in remission duration between the patients in the liposomal daunorubicin and cytarabine treatment group and the 7 + 3 treatment group. The median remission duration in the liposomal daunorubicin and cytarabine treatment group was 6.93 months (95% CI, 4.60 to 9.23) compared with 6.11 months (95% CI, 3.45 to 8.71) in the 7 + 3 treatment group (HR = 0.77; 95% CI, 0.47 to 1.26; 1-sided log-rank test P = 0.147).

The percentage of patients receiving an HSCT in the liposomal daunorubicin and cytarabine treatment group was 34% and was 25% in the 7 + 3 treatment group. There was no statistically significant difference reported in the proportion of patients who received an HSCT between the liposomal daunorubicin and cytarabine treatment group and the 7 + 3 treatment group (OR = 1.54; 95% CI, 0.92 to 2.56; 1-sided P = 0.049).

HRQoL was not assessed in Study 301.

Harms Results

All patients included in Study 301 experienced at least 1 adverse event (AE). Similarly, serious adverse events (SAEs) were comparatively common across both groups, with 59% of patients in the liposomal daunorubicin and cytarabine treatment group experiencing an SAE and 43% of patients in the 7 + 3 treatment group experiencing an SAE. The nature of the SAEs was relatively consistent between treatment arms, although sepsis occurred with twice the frequency in the liposomal daunorubicin and cytarabine treatment group (7.8%) compared with the 7 + 3 treatment group (3.3%).

Most harms of special interest occurred with similar frequency in the treatment arms; the proportion of patients who experienced an event varied depending on the type of event. A greater proportion of patients who received 7 + 3 were admitted to the intensive care unit (ICU) (25.2%) compared with patients who received liposomal daunorubicin and cytarabine (18.3%). However, the duration of ICU stay was longer for patients who received liposomal daunorubicin and cytarabine (mean ICU stay duration was 8.2 days; SD = 9.69) compared with patients who received 7 + 3 (mean ICU stay duration was 6.9 days; SD = 4.85), although the median duration of ICU stay was the same (6 days) between treatment arms.

Critical Appraisal

A dynamic balancing randomization algorithm was used for Study 301 to ensure that the assignment of treatments was balanced across all the stratification factors. However, because it was an open-label trial, patients were aware of their treatment allocation following randomization. Therefore, the evaluation of AEs may be biased by treatment knowledge.

Overall, no differences between the treatment arms in Study 301 were noted with regards to dropout rates. The statistical analyses were pre-specified and powered adequately. Many outcomes identified as significant to the patient and clinician groups were reported within the study, and the outcomes used were similar to those used in other clinical trials and close to the criteria routinely used in practice across Canada. The patient population recruited was considered representative of high-risk Canadian patients, and the associated response to conventional therapy (7 + 3) for efficacy and safety outcomes was noted by the clinical experts to be similar to that observed in practice. The trial only recruited patients who were 60 years to 75 years of age; therefore, there is uncertainty whether the results from Study 301 are generalizable to younger or older patients who may be eligible for treatment with liposomal daunorubicin and cytarabine.

An important limitation of these findings is the lack of HRQoL assessment. HRQoL was noted to be an important outcome by the patient and clinician groups who provided input to CADTH for this submission; hence, the effect of liposomal daunorubicin and cytarabine on HRQoL is uncertain. Similarly, measurable residual disease was noted to be an informative measure in determining post-transplantation survival; however, measurable residual disease was not calculated in Study 301. As such, an assessment of the comparative efficacy of liposomal daunorubicin and cytarabine relative to 7 + 3 is not possible for these outcomes.

Indirect Comparisons

No indirect comparison was performed for this review. A feasibility assessment was provided by the sponsor. The sponsor used a non-systematic literature review process but did not identify any studies that would be appropriate to analyze using indirect treatment comparison methods. The studies varied with regard to patient inclusion and exclusion criteria, and the

provided treatments did not overlap. An important limitation of this feasibility assessment is the non-systematic nature of the evidence identification process, which was not described in sufficient detail to formally assess. As such, there is uncertainty about whether all appropriate evidence has been identified for indirect comparisons.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (initiated with a decision tree)
Target population	Adults with newly diagnosed therapy-related acute myeloid leukemia or AML with myelodysplasia-related changes
Treatment	Liposomal daunorubicin and cytarabine
Submitted drug price	Daunorubicin and cytarabine liposome: $7,774.62 per package containing one 100 mL vial; each vial contains 44 mg of daunorubicin and 100 mg of cytarabine.
Cost per course	$46,642 for first induction cycle, $31,094 for a second induction cycle, and $31,094 for each consolidation cycle.
Comparator	7 + 3 (conventional 7 days of cytarabine plus 3 days of daunorubicin)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, life-years
Time horizon	15 years
Key data source	Study 301
Submitted results	ICER = $85,832 per QALY (incremental costs: $76,418, incremental QALYs: 0.89)
Key limitations	• Relevant comparators, including FLAG-IDA or 7 + 3 plus midostaurin for patients with a *FLT3* mutation, were not included in the sponsor's model. The cost-effectiveness of liposomal daunorubicin and cytarabine relative to these comparators is unknown. • Comparative clinical effectiveness was subject to uncertainty from multiple sources. In addition to structural uncertainty contributed by the modelling approach used, the sponsor used parametric survival curves to extrapolate the trial data over the time horizon of the model using separate curves for liposomal daunorubicin and cytarabine and 7 + 3 for each clinical pathway (i.e., by response and transplant status). The use of multiple overall survival and event-free survival curves increased the overall uncertainty of the model.

Component	Description
	• The sponsor assumed a greater disutility from induction and consolidation with 7 + 3 compared with liposomal daunorubicin and cytarabine, and a post-transplant remission health state value that assumed no complications. These assumptions do not align with feedback from clinical experts consulted by CADTH for this review and may overestimate the incremental benefit of liposomal daunorubicin and cytarabine. • The sponsor assumed that 70% of patients receiving consolidation therapy with liposomal daunorubicin and cytarabine would receive it in an outpatient setting compared with 40% of patients receiving 7 + 3 therapy. This difference in outpatient consolidation is not expected to occur in clinical practice. • Literature-based estimates suggest mortality is higher for patients' post-transplant. The sponsor assumed that patients who received an HSCT would experience the same background mortality rate as that of the general population, which overestimates the benefit post-transplant. • The sponsor's model was based on the characteristics of the patient population included in Study 301, which included patients 60 to 75 years of age. The cost-effectiveness of liposomal daunorubicin and cytarabine in patients < 60 years of age or > 75 years of age who are otherwise eligible for treatment is unknown.
CADTH reanalysis results	• CADTH reanalysis included alternate assumptions for the parametric OS curves used in the model, changes to the health state utility value for post-HSCT remission, changes to the disutility associated with an induction and consolidation cycle of liposomal daunorubicin and cytarabine, reduced the percentage of patients anticipated to receive outpatient consolidation for liposomal daunorubicin and cytarabine, and increased the risk of post-HSCT mortality. CADTH was unable to address uncertainty associated with the omission of relevant treatment comparators and the appropriateness of the modelled patient population (i.e., lack of inclusion of patients aged < 60 years or > 75 years). • In the sequential analysis, liposomal daunorubicin and cytarabine was associated with an ICER of $110,283 per QALY compared with 7 + 3 (incremental cost = $84,730; incremental QALYs = 0.77) • Liposomal daunorubicin and cytarabine had a 0.2% chance of being cost-effective at a cost-effectiveness threshold of $50,000 per QALY. A price reduction of at least 68% is needed for liposomal daunorubicin and cytarabine to be cost-effective compared with 7 + 3 at a cost-effectiveness threshold of $50,000 per QALY. • Cost-effectiveness was particularly sensitive to the choice of parametric survival curves.

AML = acute myeloid leukemia; FLAG-IDA = fludarabine, high-dose cytarabine, granulocyte-colony stimulating factor, and idarubicin; HSCT = hematopoietic stem cell transplantation; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: using Quebec drug prices for comparator agents, excluding relevant comparators, underestimating the incidence of AML in Canada, underestimating the market share assumed for years 2 and 3, including drug costs administered in hospital, and assuming different percentages of patients would receive outpatient consolidation therapy for liposomal daunorubicin and cytarabine.

The CADTH reanalysis included revisions to the incidence of AML in Canada, assumed market share, and percentage of patients receiving outpatient therapy, and excluded in-hospital drug costs.

The sponsor's results suggested the introduction of liposomal daunorubicin and cytarabine would lead to a budget impact of $4,408,784 in year 1, $6,252,389 in year 2, and $8,141,761 in year 3, with a 3-year budgetary impact of $18,802,933. The CADTH reanalysis estimated the budget impact to be $355,685 in year 1, $828,692 in year 2, and $1,167,732 in year 3. Three

years after entering the market, the total anticipated budget impact of liposomal daunorubicin and cytarabine is $2,352,109. The results of the CADTH reanalysis were primarily driven by the exclusion of the costs of liposomal daunorubicin and cytarabine when given in hospital. CADTH conducted a scenario analysis in which the costs of liposomal daunorubicin and cytarabine were included when given on an inpatient basis, which resulted in a 3-year budget impact of $34,304,171.

Members of the pCODR Expert Review Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: June 10, 2021

Regrets: None

Conflicts of interest: None